REMARKS

A check for $905.00 the requisite fees for a three-month extension of time and for filing a Request for Continued Examination (RCE) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1, 3, 4, 6, 7, 8-11, 13, 14, 15, 17-38, 40-46 and 48-64 are pending. Claims 2, 5, 12, 39 and 47 are cancelled herein without prejudice or disclaimer. Claims 1, 3, 4, 8, 6, 10, 17, 21, 26 and 35 are amended herein. The claims are amended to more distinctly claim the subject matter and find basis in the specification, for example, at page 6, lines 9-20, at page 31, line 23 to page 32, line 14 and in original claims 2 and 35.

Solely in the interest of advancing prosecution of this application, Claims 1, 8, 17 and 35 also are amended herein to specify particular progestational agents. Basis for the amendments can be found in original Claims 1, 6, 8, 13, 17, 25, 35 and 48 and in the specification, for example, at page 10, line 29 to page 11, line 26. No new matter is added. Applicant reserves the right to file divisional and/or continuation applications to cancelled or unclaimed subject matter.

The amendment filed August 14, 2006, responsive to the previous Office Action is incorporated by reference herein.

CITATION OF REFERENCES

In the previous Office Action mailed February 13, 2006, the Examiner alleged that the Information Disclosure Statement filed October 5, 2004, was extensive and contained irrelevant documents that allegedly hampered the ability to identify patents and publications of particular relevance. The Examiner further invited Applicant to point to documents of particular relevance. In response, Applicant noted that the submitted Information Disclosure Statement was fully complaint with the guidelines in accordance with MPEP Section 2001.04 and Rule 37 CFR §1.56, with no further action required on Applicant's part.

In the instant Final Office Action, the Examiner states that, contrary to Applicant's assertion, there was "no comment or suggestion in the prior Office Action on applicant's compliance with applicant's duty to disclose information material to patentability." The Examiner however goes on to state that "based on applicant's response, applicant has either

declined invitation, or sees no need, to aid examination by pointing to any other documents of particular relevance not cited by examiner."

Applicant respectfully takes exception to the aforementioned characterization of Applicant's previous response. As noted in the previous response, Applicant has fully complied with the requirements of the duty of disclosure, and the Examiner has provided no evidence to the contrary. It is not incumbent upon Applicant to "aid examination" beyond satisfying the duty of disclosure as set forth in .37 CFR §1.56. In fact, as noted previously by Applicant, according to MPEP Section 2001.04, patent applicants are advised to "submit information **for consideration by the Office in applications rather than making and relying on their own determinations of materiality**." (emphasis added) This is precisely what Applicant has done. It is contrary to the policies and rules set forth by the Patent Office to invite Applicant to "aid in examination" of their application by assessing materiality. Furt

Applicant takes strong exception to any suggestion by the Examiner that there is a failure to cooperate with the Patent Office in assisting examination of the application. As noted in the previous response and above, Applicant and Applicant's representative have diligently endeavored to comply with the duty to disclose information material to patentability as set forth under 37 C.F.R. §1.56 and interpreted by the U.S. Patent and Trademark Office in Section 2001.04 of the Manual of Patent Examining Procedures. The Examiner is reminded that MPEP § 2001.04 states:

> The definition of materiality in 37 CFR § 1.56 does not impose substantial new burdens on applicants, but is intended to provide the Office with the information it needs to make a proper and independent determination on patentability. **It is the patent examiner who should make the determination** after considering all the facts involved in the particular case. [emphasis added]

Applicant also directs the Examiner's attention to MPEP § 2001.05, which states:

> Under the rule, information is not material unless it comes within the definition of 37 CFR 1.56(b)(1) or (2). If information is not material, there is no duty to disclose the information to the Office. Thus, it is theoretically possible for applicants to draft claims and a specification to avoid a prima facie case of obviousness over a reference and then to be able to withhold the reference from the examiner. The Office believes that most applicants will wish to submit the information, however, even though they may not be required to do so, to strengthen the patent and avoid the risks of an incorrect judgment on their part on materiality or that it may be held that there was an intent to deceive the Office.

Applicant and Applicant's representative have diligently endeavored to provide the Office with the information that could be considered material. The Office is reminded that

the standard for disclosure set by the Courts is quite rigorous, and Applicant and the undersigned are cognizant of the case law. It is not incumbent upon Applicant, and in fact is contrary to the policies and rules set forth by the Office, to require Applicant to assist the Examiner in making determinations as to materiality and patentability; materiality and patentability are legal determinations within the purview of the role of the Office. Applicant and Applicant's representative have endeavored to be in complete compliance with the duty of disclosure as set forth in the Patent Rules, and in accordance with the guidelines provided in the Manual of Patent Examining Procedure, by providing the Office with information for consideration rather than making and relying on their own determinations of materiality.

As dictated by the Patent Rules in 37 CFR §1.97(h), the filing of an information disclosure statement shall not be considered to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in 37 CFR §1.56. Furthermore, Applicant is unaware of any requirement in complying with the duty of disclosure to particularly point out references that are definitely pertinent to the claimed invention, especially in view of the revision of the former rule that required applicants to provide a statement of the relevance of information listed in an information disclosure statement.

Applicant and the undersigned take their duty of candor very seriously and in no way have attempted to bury or otherwise hide prior art or information from the Office, nor have they been uncooperative with the Patent Office in violation of **any** duty. The undersigned has systematic procedures to ensure that all information that may be material to patentability on any basis is provided to the Office.

In the instant application, Applicant has submitted in information disclosure statements and on PTO-1449 forms information that may be relevant to the patentability of the instant claims. Applicant met its duty of disclosure to the Office when it provided information for the Examiner's consideration; contrary to the Examiner's implications, there is no additional duty to "aid examination." See, *Molins PLC, supra*. Furthermore, the mere fact of submission of a large number of references has not been found to constitute an attempt to bury (*Molins PLC*, 48 F.3d at 1184). The undersigned assures the Office that there is no such attempt here.

Finally, Office rules and procedures require that the Examiner not comment upon duty of disclosure issues. See, *e.g.*, MPEP 2010:

> ...the Office does not investigate and reject original or reissue applications under 37 CFR 1.56. Likewise, the Office ***will not comment*** upon duty of disclosure issues. . . such issues are ***no longer considered*** by the Office during its examination of patent applications. (emphasis added)

Therefore, notwithstanding the fact that Applicant has not breached its duty of disclosure, as discussed above, it is respectfully submitted that the comments made in the previous Office Action and in the instant Final Office Action are inappropriate and should be withdrawn.

THE REJECTION OF CLAIMS 1-5, 7-12, 15, 17-24, 26-44, 47 AND 49-64 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-5, 7-12, 15, 17-24, 26-44, 47 and 49-64 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make and/or use the claimed subject matter. The Examiner states that, notwithstanding Applicant's arguments to the contrary, there are large differences among the many agents considered to be progestational, and the effects of several of these agents allegedly are "unknown" and "unpredictable" because only specific agents, namely, progesterone, 17 α-hydroxyprogesterone and omega-3 fatty acids, have been tested and shown to be able to prolong a pregnancy at risk for preterm delivery.

The above rejection is rendered moot with respect to Claims 2, 5,12, 39 and 47, which are cancelled herein. With respect to the remaining claims, Applicant respectfully disagrees. As evidenced by the teachings of the specification and the numerous publications of record, the mechanism of action of progestational agents was known to those of skill in the art as of the instant application's earliest priority date (in fact as early as the mid-1970's), as were assays to test for their ability to delay delivery in subjects at risk for preterm delivery. To satisfy the standard for enablement, it is not necessary for the claims to specifically exclude inoperative substances. Rather, the question is whether by following the teachings of the application, one of skill in the art can practice what is claimed with perhaps routine, but not undue, experimentation. Applicant respectfully submits that by following the teachings of the application, in combination with the extensive knowledge in the art regarding progestational agents and their ability to delay delivery, one of skill in the art can readily identify suitable progestational agents for use in preventing preterm delivery.

Notwithstanding the above, in the interest of advancing prosecution of this application, Applicant has amended the claims herein to specify that the progestational agent is selected

from among progesterone, 17 α-hydroxyprogesterone, 17 α-hydroxyprogesterone caproate and omega-3 fatty acids, with dependent claims 7, 14 and 46 specifying that the omega-3 fatty acid is docosahexanoic acid. As the Examiner has noted, the aforementioned progestational agents were known to those of skill in the art as of this application's effective filing date as being effective in preventing preterm delivery. Further, as Applicant pointed out in the previous response filed August 14, 2006, which is incorporated by reference herein, the specification provides extensive teachings which, when coupled with the knowledge of those of skill in the art regarding the ability of these particular progestational agents to prevent preterm delivery, renders the claims enabled for their full scope.

The claims as amended herein are directed to combinations and methods that use progestational agents that are known to delay delivery, and such is acknowledged by the Examiner. The progestational agents themselves are known, as is their ability to delay delivery. The instant claims specify combinations and methods in which these known progestational agents are administered to subjects who are identified as being at risk for preterm delivery based on the level of one or more markers of preterm delivery and/or membrane rupture in samples taken from the subjects. Thus, it respectfully is submitted that the claims as amended herein are enabled for their full scope. Accordingly, reconsideration and withdrawal of this rejection respectfully is requested.

THE REJECTION OF CLAIMS 35-64 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 35-64 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in a manner that would suggest to one of skill in the art that applicantion had possession of what is claimed. In particular, it is alleged that while one of skill in the art "might realize from reading the disclosure" that sequential determinations [of markers] are useable," there is no "explicit or implicit" support for such a sequential method.

Applicant respectfully submits that to evidence possession of what is claimed, it is not necessary for the subject matter to be disclosed *in haec verba*. . *See e.g.* In re Herschler, 591 F.2d 693, 700, 200 USPQ 711, 717 (CCPA 1979); Purdue Pharma L.P. v Faulding, Inc. 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Nonetheless, the rejection is rendered moot herein by amending the claims so that they no longer recite the sequential assessment of markers.

REJECTION OF CLAIMS 1-7, 10, 11, 15 AND 17-64 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-7, 10, 11, 15, 21 and 29 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Each of the ground of rejection are addressed in turn below:

Claims 1-7 are rejected as allegedly being indefinite because no components of the test system are recited. The rejection is addressed herein by amending Claim 1 to incorporate the limitations of Claim 2 and recite that the test system includes an antibody that binds to a fetal-restricted antigen or to estriol.

Claim 4 is rejected as providing no further limitation of the combination by reciting the types of samples for its intended use. Claim 4 is amended herein to specify that the combination further contains a sample-collecting device to collect the recited samples.

Claims 10, 11 and 15 are rejected as allegedly unclear because the interrelationships of the further antibodies to the anti-(preterm delivery marker) on a solid support are not specified. Applicant respectfully submits that the metes and bounds of the rejected claims, in light of the disclosure in the specification, are clear. As the specification clearly discloses, for example, at page 5, line 23 to page 6, line 8, the combinations that are the subject matter of the instant claims can contain antibodies against one or more markers, including markers of preterm delivery, fetal-restricted antigens and markers of membrane rupture, and a progestational agent. The cited passage further recites that the one or more antibodies can be immobilized, conjugated or unconjugated to a solid support. Thus, the metes and bounds of Claims 10, 11 and 15, which specify that the combination of Claim 8 contains antibodies in addition to the anti-(preterm delivery marker) antibody on a solid support as specified in Claim 8, are clear.

Claim 21 is rejected as allegedly unclear because "the" ratio lacks antecedent basis. Claim 21 is amended herein to clarify that the ratio, *i.e.*, the marker of Claim 17, is monitored by measuring the levels of estriol and progesterone in the body fluid sample from the subject, then determining their ratio. Basis for this amendment can be found in the specification, for example, at page 31, line 23 to page 32, line 14, which describes the value of the ratio of estriol to progesterone as a known marker for preterm delivery.

Moreover, the quotient of any two numbers results in a single result – the ratio. Accordingly, it is appropriate to refer to the quotient of any two numbers as the ratio. Thus, the scope of the claim as amended herein would be reasonably ascertainable by those skilled in the art. Hence, the claim is not indefinite.

Claim 39 is rejected as allegedly indefinite because the recitation "*the* start of fetal organogenesis" allegedly lacks antecedent basis. This rejection is rendered moot by cancellation of Claim 39 herein.

THE REJECTION OF CLAIMS 1-13, 17-19, 22-26, 30, 31, 33 AND UNDER 35 U.S.C. §103(a)

Claims 1-13, 15-19, 22-26, 30, 31, 33-44 and 47-64 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Leavitt *et al.* (WO 94/17405) in view of any of Johnson *et al.* (NEJM 293: 675, 1975), Meis *et al.*, (Am J Obstet Gynecol 187: S54, 2002) or Keirse (Br J Obstet Gynecol 97: 149, 1990) and further in view of Weiner *et al.* or Andersen *et al.* The Examiner states that, notwithstanding Applicant's arguments to the contrary, Leavitt *et al.* allegedly teaches the determination of biochemical markers of imminent or preterm delivery to aid in clinical decisions regarding the administration or treatments, and the remaining references allegedly teach that the treatment can be a progestational agent. The Examiner alleges that any of Johnson *et al.*, Meis *et al.* or Keirse teaches the efficacy of progesterone treatments in reducing preterm delivery and that Weiner *et al.* or Andersen *et al.* teaches that treatment with tocolytic agents is not beneficial in patients with membrane rupture. The Examiner alleges that one of ordinary skill in the art would have tested a pregnant patient determined to have biochemical markers indicative of impending preterm delivery for the status of the fetal membranes and to treat those patients with intact fetal membranes indicated as at risk for having impending delivery with a pregnancy-prolonging agent because of the direct suggestion in Leavitt *et al.* to do so. The Examiner further alleges that it would have been obvious to treat a patient so identified with a known efficacious pregnancy-prolonging agent such as progesterone in light of the teachings of any of Johnson *et al.*, Meis *et al.* or Keirse. The Examiner also alleges that Applicant improperly traversed the rejection by attacking the references individually. This rejection is respectfully traversed.

As a preliminary matter, Applicant respectfully submits that, in responding to the rejections under 35 U.S.C. §103(a) in the previous response filed August 14, 2006, **Applicant**

did not attack the references individually. Rather, Applicant described the teachings of each reference, then argued that the combination of the references does not result in the claimed subject matter. As discussed below, each of the cited references teaches either (1) methods of diagnosing preterm delivery; or (2) methods of treating preterm delivery; or (3) that a variety of diagnostic markers and a variety of treatments are available to diagnose and/or detect preterm delivery. None of the references, singly or in any combination, teaches or suggests selection of the particular combination of identifying subjects at risk for preterm delivery based on detection of biochemical marker(s) for preterm delivery, such as a fetal-restricted antigen or estriol or a marker for membrane rupture, for treatment with a progestational agent.

Applicant respectfully submits that in setting forth the rejections on obviousness grounds, the Examiner is employing hindsight, combining numerous references, each of which teaches one or part of one element of the claimed combinations and methods. As discussed below, it is the selection of a particular diagnostic (detection of a biochemical marker for preterm delivery), for treatment with a particular therapeutic for preterm delivery (progestational agent), that is taught by the instant application and is not taught or suggested by any of the cited references, singly or in any combination.

RELEVANT LAW

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ

871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 1 and dependents are directed to a combination containing a test system for detecting a fetal-restricted antigen or estriol that contains antibodies to the fetal-restricted antigen or estriol, and a progestational agent that is selected from among progesterone, 17-α-hydroxyprogesterone, 17-α-hydroxyprogesterone caproate and an omega-3 fatty acid.

Claim 8 and dependents are directed to a combination for screening and treating a subject that includes a solid support containing an anti-(preterm delivery marker) antibody; and a progestational agent that is selected from among progesterone, 17-α-hydroxyprogesterone, 17-α-hydroxyprogesterone caproate and an omega-3 fatty acid.

Claim 17 and dependents are directed to a method of screening and treating a subject by monitoring the level of a marker of preterm or imminent delivery in a body fluid sample from a subject, and if the level is indicative of a risk for preterm or imminent delivery, administering a progestational agent to delay delivery, where the agent is selected from among progesterone, 17-α-hydroxyprogesterone, 17-α-hydroxyprogesterone caproate and an omega-3 fatty acid.

Claim 26 and dependents are directed to a method of screening and treating a subject by monitoring the level of a first marker and a second marker of preterm or imminent delivery in a body fluid sample from a subject; if the level of the first marker is indicative of a risk for preterm or imminent delivery, evaluating the level of the second marker; and if the level of the second marker is indicative of a risk for preterm or imminent delivery, administering a progestational agent to delay delivery, where the agent is selected from among progesterone, 17-α-hydroxyprogesterone, 17-α-hydroxyprogesterone caproate and an omega-3 fatty acid.

TEACHINGS OF THE CITED ART

Leavitt *et al.* (WO 94/17405)

Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery having intact membranes, from those in whom the membranes have ruptured. Leavitt et al. teaches that patients with clinically intact membranes should be tested for biochemical markers and/or a variety of other factors indicative of a risk of preterm delivery (page 6, lines 16-34), to identify "patients susceptible to treatments to delay delivery." (page 4, lines 33-36). Leavitt *et al.* teaches that one biochemical marker for imminent delivery is fetal fibronectin and that the presence of an elevated fibronectin level in the sample indicates an increased risk of imminent delivery (*e.g.*, see page 4, lines 5-14).

Leavitt *et al.* does not teach or suggest the particular combination of measuring a marker for preterm delivery, such as a fetal-restricted antigen, estriol or a marker for membrane rupture, as the basis for identifying patients at risk for preterm delivery who should be administered a particular treatment, namely, a progestational agent. As discussed below, it is only the instant application that teaches the desirability of selecting this particular combination of components and/or steps for the combinations and methods as claimed.

Johnson *et al.* (NEJM 293: 675, 1975)

Johnson *et al.* teaches a possible obstetric use of 17α-hydroxyprogesterone caproate in the prevention of premature labor, in patients with a history of spontaneous abortions. Johnson *et al.* does not teach or suggest measuring a marker for preterm delivery, such as a fetal-restricted antigen, estriol or a marker for membrane rupture, as the basis for identifying patients at risk for preterm delivery, for treatment with17α-hydroxyprogesterone caproate.

Meis (Am J Obstet Gynecol 187: S54, 2002)

Meis teaches that small studies from the 1970s and 1980s suggested a benefit of 17α-hydroxyprogesterone therapy in preventing preterm birth, and a larger double-blind study was undertaken. Meis teaches that treatment with 17α-hydroxyprogesterone significantly reduced the risk of preterm birth in women at high risk. Meis, like Johnson *et al.*, relies on a patient history of spontaneous preterm delivery to identify subjects for administration of 17α-hydroxyprogesterone.

Keirse (Br J Obstet Gynecol 97: 149, 1990)

Keirse teaches a meta-analysis of controlled trials of a variety of progestational agents and concludes that there is no support that 17α-hydroxyprogesterone caproate protects against

miscarriage but suggests that it does reduce the occurrence of preterm birth. Keirse teaches that 17α-hydroxyprogesterone caproate is the most fully studied progestational agent (page 149, col. 2, last full paragraph). Keirse teaches that its study indicates that injections of 17α-hydroxyprogesterone caproate may reduce the occurrence of preterm birth among women so treated (page 153, col. 2, second full paragraph). Keirse does not teach or suggest measuring a marker for preterm delivery, such as a fetal-restricted antigen, estriol or a marker for membrane rupture, as the basis for identifying patients at risk for preterm delivery, for treatment with17α-hydroxyprogesterone caproate

Weiner *et al.* (Am J Obstet Gynecol 159: 216-222 (1988))

Weiner *et al.* teaches that preterm premature rupture of the membranes is associated with 40% of preterm deliveries (page 216, col. 1, first paragraph). Weiner *et al.* teaches that bed rest is generally accepted as the preferred management for the uninfected patient with preterm premature rupture of the membranes who is not in labor (*Id.*). Weiner *et al.* teaches that many physicians refrain from the use of tocolytic agents in women with preterm premature rupture of the membranes because tocolytic agent efficacy and safety in this subgroup are not clear (*Id.*). Weiner *et al.* teaches that tocolysis for preterm labor preceded by rupture of membranes are directed to delaying delivery only to administer corticosteroids in the hope of accelerating fetal lung maturity (*Id.*). Weiner *et al.* teaches that the use of tocolysis for preterm labor associated with intact membranes improves neonatal outcome (page 221, col. 1, first paragraph). Weiner *et al.* teaches that treatment of labor after preterm premature rupture of the membranes does not improve perinatal outcome after 28 weeks gestation (page 222, first paragraph).

Weiner *et al.* is virtually of no relevance to any of the instant claims. The instant claims are directed to methods and products for screening and treating women at risk of preterm delivery with progestational agents. Weiner *et al.* is concerned with women with ruptured membranes and the use of tocolytic agents, not progestational agents, for treatment of such subjects. Weiner *et al.* provides no teaching or suggestion regarding the identification of subjects at risk for preterm delivery by measuring a biochemical marker, nor of administering a progestational agent to subjects so identified.

Andersen *et al.*

Andersen *et al.* teaches that preterm labor is a major problem in obstetrics, and that about a third of preterm births are associated with preterm premature rupture of membranes (PROM) (page 336, col. 1, second full paragraph). Andersen *et al.* teaches that in some instances preterm labor follows PROM, while in other situations preterm delivery becomes medically indicated because of the development of infection or other pregnancy complications (*Id.*). Andersen *et al.* suggests that progesterone withdrawal plays an important role in the onset of labor, finding lower progesterone levels in patients in preterm labor than in normal controls but that prostaglandins play a more important role in the onset of labor (page 337, col. 2, second and third paragraphs). Andersen *et al.* teaches that progesterone injections have been suggested to prevent preterm delivery, but are ineffective at stopping established preterm labor (page 345, col. 2, fourth paragraph). Andersen *et al.* teaches that weekly injections of 17α-hydroxyprogesterone caproate is used in prophylactic therapy in women at high risk for preterm delivery (*Id.*). Andersen *et al.* teaches that the diagnosis of preterm PROM is made by a sterile speculum examination with pooling fluid in the vaginal vault, positive Nitrazine tests and ferning of a dried smear of the fluid (page 346, col. 1, third paragraph). Andersen *et al.* that preterm labor should be treated promptly with tocolytic drugs if amnionitis or infection is not present, because once labor is more actively established treatment is less likely to be efficacious (page 349, col. 1, first full paragraph). Hence Anderson *et al.* is of little relevance to the instant claims, since it is directed to the use of tocolytic therapy and factors to consider in assessing the risk of preterm labor following premature rupture of membranes (PROM)

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of the teachings of Leavitt *et al.* and Johnson *et al.* or Meis or Keirse with the teachings of Weiner *et al.* or Andersen *et al.* does not result in the instantly claimed methods.

(1) There is a benefit to choosing a test for a preterm delivery marker fetal-restricted antigen as the diagnostic for the selection of candidates for treatment with progestational agents. Only the instant application appreciates this benefit.

Progestational agents typically are administered to prevent preterm delivery. The treatment regimen with progestational agents generally begins relatively early in pregnancy, often before any symptoms of preterm delivery become manifest. The treatment also follows

a course of several weeks, beginning at about 12-18 weeks gestation and ending at about 37 weeks or delivery, whichever comes earlier. A variety of side effects have been attributed to progestational agents, depending on the type of agent – side effects include a possible increase in the risk of fetal malformation (*e.g.*, cardiac, neurological, neural tube defects) or esophageal atresia; *see* specification at page 1, lines 27-30). Reactions in the mother can include those occurring at the site of injection (*e.g.*, upon intramuscular injection of progesterones) such as pain, swelling, bruising or other allergic reaction at the site of injection, and other side effects such as headache, nausea, breast swelling and tenderness, coughing, and difficulty in breathing.

Thus, in selecting subjects for treatment with progestational agents, it is important to choose a diagnostic for preterm delivery that: (a) can be used to diagnose subjects at risk for preterm delivery relatively early in the pregnancy; so that treatment with progestational agents can be initiated and (b) is accurate, *i.e.*, the likelihood of identifying "false positive" candidates who unnecessarily are administered a multi-week treatment regimen, or the likelihood of missing candidates at risk in whom preterm delivery could have be prevented by early intervention using progestational agents, is low. It is only the instant application that appreciates the benefit of selecting a test for a fetal-restricted antigen, such as fetal fibronectin or estriol, as the preterm delivery diagnostic of choice that fulfils criteria (a) and (b) for identifying suitable subjects for treatment with progestational agents.

(2) Conversely, when a subject has been identified as being at risk for preterm delivery based on the level of a fetal-restricted antigen and before any symptoms of preterm delivery become manifest, there is a benefit to choosing a treatment that can be administered early to prevent preterm delivery. Only the instant application appreciates the benefit of treating subjects thus identified with a progestational agent.

As discussed in detail below, a test for a biochemical marker for preterm delivery including a fetal-restricted antigen, such as fetal fibronectin or estriol, identifies subjects at risk for preterm delivery with a higher accuracy and earlier in the pregnancy than other tests. Therefore, the test for a fetal-restricted antigen is poised for combination with a treatment that can be administered to prevent preterm delivery, relatively early in the pregnancy, before symptoms become manifest. Treatment with progestational agents provides this benefit in a way that other treatments for preterm delivery, such as tocolytic agents, do not. It is the instant application that appreciates the benefit of this combination.

Detailed Analysis

It is clear from the above summary that not every test assessing a risk for preterm delivery is the same, nor is every treatment regimen the same. For example, if a subject is experiencing premature contractions, a possible indication of preterm delivery, a short term treatment with a tocolytic may be administered for a few days to stop the contractions and permit further observation and care. On the other hand, if a subject is identified as being at risk for preterm delivery before any symptoms become manifest, the reliability of the test becomes more important as one would not unnecessarily want to expose the subject to treatment with drugs. In addition, when a subject is treated for preterm delivery before symptoms become manifest, it likely is desirable to administer a treatment that is more in the nature of a preventative, like a progestational agent, as opposed to a tocolytic agent that is used when contractions are present. This message is borne out in a recent article by Ables *et al.* (*J. Fam. Practice*, 54:3 (2005); of record in the Information Disclosure Statement accompanying this amendment and RCE), which, while not provided herein to demonstrate operativeness of the claimed combinations and methods, describes how when it comes to preterm delivery, not all diagnostic and therapeutic options are alike.

It is the instant application that appreciates the particular combination of a diagnostic for preterm delivery that is based on detection of a marker for a fetal-restricted antigen, with a therapeutic such as a progestational agent that permits intervention and prevention of preterm delivery, and its use in methods of screening and treating subjects at risk for preterm delivery. As discussed below, a test for a fetal-restricted antigen permits one of the most reliable and accurate assessments of the risk for preterm delivery, beginning relatively early in the pregnancy (12-16 weeks). This assessment then identifies candidates for treatment with a progestational agent, without the accompanying concern that a multiple week regimen to prevent preterm delivery is needlessly being administered to someone who in fact is not at risk for preterm delivery. Nowhere in the prior art, singly or in any combination, is there a teaching or suggestion of such a combination or method using this particular combination of diagnostic and therapeutic.

The rejected claims are directed to combinations and methods in which components a) an antibody or a test system for detecting the presence of one or more markers for preterm delivery (fetal-restricted antigen or estriol, sometimes in conjunction with the detection of

IGFBP-1) in a sample; and b) a progestational agent, examples being progesterones and omega-3 fatty acids, are used to identify subjects at risk for preterm delivery and to treat subjects so identified with a progestational agent. Not every subject identified as being at risk for preterm delivery *per se*, automatically becomes a candidate for treatment with a progestational agent to prevent preterm delivery. Rather, performing a test with component a) selects an optimal subset of subjects at risk for preterm delivery, for treatment to prevent preterm delivery using component b). The identification of subjects as being at risk for preterm delivery *per se* is not enough; the basis of the identification can determine the suitability of a subject population for treatment with progestational agents to prevent preterm delivery, which provides advantages that are not taught or suggested by any of the cited references, singly or in any combination. The selection of a particular population of subjects at risk for preterm delivery, those that are identified by a level of a biochemical marker or markers for preterm delivery, as the population best suited for treatment with progestational agents, is not taught or suggested by the cited references, singly or in any combination.

The population of subjects who are selected for administration of a progestational agent to prevent preterm delivery based on detection of biochemical marker(s) for preterm delivery, possess properties that are not taught or suggested by previous studies, singly or in any combination. It is only the instant application that teaches selection of such a population.

When selecting a population for treatment to prevent preterm delivery, the parameters that form the basis for such selection must be taken into account. Previous studies have used parameters such as a history of spontaneous preterm delivery, spontaneous abortions and/or miscarriages to identify subjects for treatment to prevent preterm delivery. These parameters have proved far from ideal in identifying the population best suited for such treatment. For example, patients with a history of spontaneous abortions or miscarriages generally are not responsive to treatment with progestogens, including progesterones (*see, e.g.*, Keirse, *Br. J. Obstet. Gynecol.*, 97:149-154 (1990); of record).

Other studies have used a history of spontaneous preterm delivery as the basis for selecting subjects for treatment with progesterones (*see, e.g.*, Meis, *Am. J. Obstet. Gynecol.*, 187:554 (2002) and an elaboration of the same study in Meis *et al.*, *New Engl. J. Med.*, 348(24):2379-2385 (2003); of record). Although these studies demonstrated some benefit of administering the progesterones for delaying delivery, the rate of preterm delivery still

remained very high, with at most one in every five or six treated women actually benefiting from the treatment (the others either did not benefit from the treatment or would not have had a preterm delivery regardless of the treatment). For the women who would not have had a preterm delivery in their current pregnancy, regardless of their past history, these studies also meant unnecessary administration of a drug that is known to have associated side effects.

The selection of a subset of subjects based on *past* spontaneous preterm deliveries, for treatment to delay their *current* pregnancy, poses the additional problem of not taking into consideration the vast majority of women at risk for preterm delivery, *i.e.*, those who have had no previous preterm delivery (*see, e.g.*, Meis *et al.* (2003)). It is only the instant application that teaches optimizing the population of "at risk" women selected for treatment with a progestational agent by (1) selecting women based on identification of the pregnancy *at issue* as being at risk for preterm delivery, regardless of their classification as "high risk" or "low risk" based on past delivery history, by assaying for a biochemical marker for preterm delivery, such as a fetal-restricted antigen including fetal fibronectin or estriol, in samples taken during the current pregnancy; and (2) minimizing or eliminating from the treatment pool those women who are not at risk for preterm delivery in their current pregnancy, regardless of their past history.

Furthermore, it is the instant application that teaches using a test for assessing the risk of preterm delivery in the current pregnancy, before any symptoms become manifest, which (a) can be used relatively early in the pregnancy; and (b) is accurate. The test for a fetal-restricted antigen satisfies (a) and (b), characteristics that are optimal for the selection of candidates for treatment with a progestational agent (often a multi-week treatment regimen beginning relatively early in the pregnancy, for which it is important to determine the risk of preterm delivery before clinical symptoms become manifest, and for which it is important to avoid unnecessary administration to subjects not in need of treatment).. As discussed in the article by Ables *et al.*, the current standard for assessing risk of preterm delivery in the pregnancy at issue, without regard to past pregnancies, is based on a physical diagnosis assessing uterine contractions before 37 weeks and a change in cervical dilation or effacement as measured by digital examination. As Ables *et al.* describes, such a physical diagnosis can suggest a risk for preterm delivery when it is absent, or miss identifying a risk when it is present. It is the instant application that teaches the particular compatibility of a

test for detecting a fetal-restricted antigen to identify subjects at risk for preterm delivery, and a progestational agent to prevent preterm delivery. Nowhere in the cited art, singly or in any combination, is there a teaching or suggestion of the desirability of this particular combination, nor the benefits derived from the combination.

Combination of Cited References

Thus, Leavitt *et al.* does not teach or suggest a combination nor a method that includes components or steps for detecting a fetal-restricted antigen, estriol or other biochemical marker(s) in a sample to identify subjects at risk for preterm delivery, and a progestational agent to treat subjects so identified. Leavitt *et al.* teaches assays and other risk factors that distinguish between subjects with impending immediate delivery with intact membranes from those in whom the membranes have ruptured. Nowhere does Leavitt *et al.* teach or suggest administering a progestational agent as the treatment of choice, much less administering it to the particular subset of subjects in whom the risk of preterm delivery is measured by a biochemical marker. Johnson *et al.*, in which risk of preterm delivery is assessed by a history of spontaneous abortions, does not cure these deficiencies. Johnson *et al.* teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in patients categorized as high-risk based on a past history of spontaneous abortions. As discussed above, past history is not the most reliable indicator of the best population of subjects for treatment with a progestational agent. Similarly, Meis and Keirse also do not teach or suggest the use of a progestational agent in a subject population identified as being at risk for preterm delivery based on measuring the level of one or more biochemical markers for preterm delivery in their current pregnancy. Meis teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in women with a documented history of a previous spontaneous preterm birth. Keirse teaches that 17α-hydroxyprogesterone caproate reduces the occurrence of preterm birth in women considered to be at high risk of preterm delivery, but does not teach or suggest testing the subjects to determine whether they are at risk for imminent or preterm delivery in their current pregnancy. As discussed above, it is the instant application that appreciates the desirability of selecting the particular population of subjects identified as being at risk for preterm delivery based on detection of a biochemical marker for preterm delivery, for administration of a progestational agent. Thus, Meis and Keirse also do not cure the deficiencies of Leavitt *et al.*

Furthermore, Applicant respectfully submits that neither Weiner *et al.* nor Andersen *et al.* teaches or suggests the missing elements of the combination of the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse. Neither of these references teaches or suggests testing women for detecting a biochemical marker, such as a fetal-restricted antigen or estriol, as the basis for identifying subjects at risk for preterm delivery for administration of a progestational agent, nor administration of a progestational agent. Hence, none of the secondary references, singly or in any combination, cure the deficiencies of Leavitt *et al.*

As discussed in detail above, the instantly claimed combinations and methods are designed to identify and treat a population at risk for preterm delivery that is most likely to respond to treatment with a progestational agent, while eliminating or at least minimizing administering the drug to those not in need of it. The combination of Leavitt *et al.*, which does not teach or suggest the selection of a particular diagnostic for preterm delivery, nor the selection of a particular treatment for preterm delivery, with any of the secondary references, which also do not teach or suggest the particular, desirable selection of progestational agents for the treatment of patients identified as being at risk for preterm delivery based on the level of a biochemical marker(s) for preterm delivery, does not result in the claimed combinations and methods. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of the rejected claims.

THE REJECTION OF CLAIMS 1-13, 15, 17-44 and 47-64 UNDER 35 U.S.C. §103(a)

Claims 1-13, 15, 17-44 and 47-64 are rejected under 35 U.S.C. §103(a) as being obvious over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.* and further in view of Dullien (U.S. Pat. No. 5,480,776). Applicant respecftully traverses the rejection.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above. Claim 35 and dependents are directed to a method of screening and treating a subject that includes detecting a fetal restricted antigen in a sample from a subject and assessing whether the level of fetal restricted antigen is indicative of a risk of preterm or imminent delivery, and if the level of fetal restricted antigen is indicative of the

risk, administering a therapeutically effective amount of a progestational agent to the subject, whereby delivery is delayed, where the progestational agent is selected from among progesterone, 17-α-hydroxyprogesterone, 17-α-hydroxyprogesterone caproate and an omega-3 fatty acid.

.TEACHINGS OF THE CITED ART

See related section above.

Dullien (U.S. Pat. No. 5,480,776)

Dullien teaches a method for detecting the onset of labor in a patient. The method includes analyzing a body fluid of the patient for estriol concentration, correlating the concentration with a standard value and relating a higher concentration of estriol relative to the standard value as an indication of potential onset of pre-term labor, where the method does not require determination of an estriol/progesterone concentration ratio in the body fluid being tested (col. 2, lines 19-33). Dullien teaches that the assay for estriol can be performed on any body fluid, and that saliva is preferred because unlike urine, detection is not complicated by the presence of estrogen conjugates (col. 2, lines 54-61). Dullien does not teach or suggest administering a progestational agent to treat subjects identified as being at risk for preterm delivery. The Examiner refers to another Dullien patent, U.S. Patent No. 5,370,135, for the proposition that Dullien does teach treatment of patients identified as being at risk for preterm delivery. The cited patent however teaches the administration of tocolytic agents, not progestational agents.

ANALYSIS

As discussed above, the particular combination of detection of a biochemical marker, such as a fetal-restricted antigen or estriol and/or a marker for membrane rupture, as indicative of a risk for preterm delivery in a subject, with a progestational agent for treating a subject so identified, is not taught or suggested by any of the cited references, singly or in any combination. Dullien *et al.*, which teaches detection of estriol but doe not teach or suggest any preferred choice of treatment for such subjects, does not cure these deficiencies. The other Dullien patent (5,370,135) referred to by the Examiner but not cited as a basis for the rejection teaches monitoring estriol for tocolytic therapy; it also contains no teaching or suggestion that administration of a progestational agent would be desirable in a population identified as being at risk for preterm delivery based on detection of a biochemical marker for

preterm delivery. As discussed in detail above, not every combination of a diagnostic and a treatment for preterm delivery is the same, and it is only the instant application that teaches the selection of a particular diagnostic for use with a particular therapeutic in the claimed combinations and methods. None of the cited references, singly or in any combination, teaches or suggest the instantly claimed combinations and methods based on identifying subjects at risk for preterm delivery based on assessing a biochemical marker for preterm delivery, for treatment with a progestational agent. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

THE REJECTION OF CLAIMS 7, 14, 17-19 and 22-26 UNDER 35 U.S.C. §103(a)

Claims 14, 45 and 46 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.* and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) or Olsen *et al.* (Lancet 339: 1003 (1992)). The Examiner alleges that the combination of the teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse and further in view of Weiner *et al.* or Andersen *et al.* teaches every element of the claims. Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above. The rejected claims all recite an omega-3 fatty acid.

TEACHINGS OF THE CITED ART

See related section above.

Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)

Allen *et al.* teaches that n-3 fatty acids may play a role in gestation and parturition. Allen *et al.* teaches that several human pregnancy supplementation trials with n-3 fatty acids have shown a significant reduction in the incidence of premature delivery and increased birth weight associated with increased gestational duration (page 498, col. 1). Allen *et al.* teaches that supplementation with long-chain n-3 fatty acids such as docosahexaenoic acid (DHA) may be useful in prolonging the duration of gestation in some high-risk pregnancy (*Id.*). Allen *et al.* teaches that a positive increase in gestational length was observed with dietary n-3 fatty acid supplementation (page 502, col. 1, second paragraph). Allen *et al.* teaches that the evidence

linking n-3 fatty acid intakes and changes in maternal n-3 fatty acid status with alterations in gestational length is strong (page 503, col. 2, last paragraph).

Olsen *et al.* (Lancet 339: 1003 (1992)

Olsen *et al.* teaches that fish oil supplementation in the third trimester seems to prolong pregnancy without detrimental effects on the growth of the fetus or on the course of labor (page 1003, col. 1, last paragraph). Olsen *et al.* teaches that a diet rich in long-chain n-3 fatty acids prolongs gestation, possibly by delaying initiation of labor and cervical ripening by inhibiting the production of prostaglandins and increasing the production of prostacyclins (page 1003, col. 2, last paragraph). Olsen *et al.* teaches that average gestation, birth weight and birth length was greatest in the fish-oil group and lowest in the olive oil group (page 1005, col. 2, first paragraph). Olsen *et al.* teaches that there is a dose-response relation up to a level of saturation between dietary fish oil and duration of gestation (page 1006, col2, first paragraph). Olsen *et al.* teaches that dietary marine n-3 fatty acids have a regulatory function in the process leading to the initiation of parturition in human beings, possibly by shifting the balance of the production of eicosanoids in favor of those derived from n-3 rather than n-6 fatty acids (page 1007, col. 1, first paragraph).

ANALYSIS

As discussed above, the particular combination of detection of a biochemical marker, such as a fetal-restricted antigen or estriol and/or a marker for membrane rupture, as indicative of a risk for preterm delivery in a subject, with a progestational agent for treating a subject so identified, is not taught or suggested by any of the cited references, singly or in any combination. Neither Allen *et al.*, nor Olsen *et al.*, each of which teaches the beneficial effects of a particular therapeutic (omega-3 fatty acids) in prolonging gestation during high risk pregnancies but not a combination of a particular diagnostic with a particular therapeutic, cures these deficiencies. There is no teaching or suggestion in either of these references regarding detection of a biochemical marker, such as a fetal-restricted antigen or estriol or a marker for membrane rupture as the basis for identifying subjects for administration of a progestational agent. Therefore, these references do not cure the deficiencies of the remaining references and the Examiner has failed to set forth a *prima facie* case of obviousness.

THE REJECTION OF CLAIMS 7, 14, 17-25, 30-34, 45 and 46 UNDER 35 U.S.C. §103(a)

Claims 7, 14, 17-25, 30-34, 45 and 46 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.*, further in view of Dullien *et al.* and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) or Olsen *et al.* (Lancet 339: 1003 (1992)).

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above. Claims 45 and 46 ultimately depend from claim 35.

TEACHINGS OF THE CITED ART

See related section above.

ANALYSIS

As discussed above, the particular combination of detection of a biochemical marker, such as a fetal-restricted antigen or estriol and/or a marker for membrane rupture, as indicative of a risk for preterm delivery in a subject, with a progestational agent for treating a subject so identified, is not taught or suggested by any of the cited references, singly or in any combination. As also discussed above, neither Dullien et al., nor Allen *et al.*, nor Olsen *et al.*, each of which teaches a particular diagnostic (detection of estriol) or the beneficial effects of a particular therapeutic (omega-3 fatty acids) in prolonging gestation during high risk pregnancies but not a combination of a particular diagnostic with a particular therapeutic, cures these deficiencies. There is no teaching or suggestion in either of these references regarding detection of a biochemical marker, such as a fetal-restricted antigen or estriol or a marker for membrane rupture as the basis for identifying subjects for administration of a progestational agent. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

Stephanie L. Seidman
Reg. No. 33,779

Attorney Docket No. 17101-025001 / 826
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com